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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,665	11/07/2005	Donald W. Kufe	00530-108US1	6843

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EXAMINER	
FRAZIER, BARBARA S	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
01/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,665	KUFE ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008 and 03 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *5-16,25,26 and 30-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,17-24 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/06,12/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-47 are pending in this application.

Election/Restrictions

2. Applicant's election without traverse of claims 17-24 and 27-29 (in part) in the reply filed on 10/3/08, and election of the species STI571 (4-[(4-Methyl- 1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2- pyrimidinyl]amino-]-phenyl]benzamide methanesulfonate) in the reply filed on 5/508, is acknowledged.

3. Claims 1-4 will be examined with the elected claims.

4. Claims 5-16, 25, 26, and 30-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 5/5/08 and 10/3/08.

5. Claims 1-4, 17-24, and 27-29 are examined.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **Claims 1-4, 17-24, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing oxidative**

stress-associated cell death, does not reasonably provide enablement for preventing oxidative stress-associated cell death. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors have been considered and those factors which are relevant to the instant fact situation are discussed below:

The nature of the invention and the relative skill of those in the art

The invention relates to the prevention of oxidative stress-associated cell death. The relative skill of those in the art is high, that of an MD or PhD.

The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "prevention" as "to keep from happening or existing", i.e., to completely eradicate. The claims are thus very broad insofar as they recite the "prevention" of oxidative stress-associated cell death, i.e., the complete eradication of same. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live, since oxidative stress-associated cell death is always occurring on some level, even in healthy individuals.

The amount of direction or guidance provided and the presence or absence of working examples

Additionally, the specification provides no direction or guidance, including no useful therapeutic protocols, for prevention of oxidative stress-associated cell death.

The latter is corroborated by the working examples.

The quantity of experimentation necessary

In the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent oxidative stress-associated cell death as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is vague and indefinite in that the metes and bounds of the phrase "evaluating the viability of a neurological or cardiovascular tissue" are unclear. The phrase is unclear because it is not clear if the "evaluating" pertains to determining the level of cell death in said tissue, or the level of functioning of said tissue (e.g., what number of cells in the heart are still viable vs. how well the heart is functioning). The specification provides no further guidance as to the definition of the phrase "evaluating the viability".

For purposes of examination, the claim shall be construed to mean the viability of cells in said tissue.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-4, 17, 18, 21-24, and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambacorti-Passerini et al (WO 01/47507, hereinafter "Gambacorti") in view of Kumar et al (J.Bio.Chem., 276(20), pp. 17281-17285, 2001, hereinafter "Kumar") and Kufe et al (US Patent 7,118,862, hereinafter "Kufe").

The claimed invention is drawn to a method of reducing or preventing oxidative stress-associated cell death, the method comprising selecting an individual diagnosed as having or being at risk of contracting a disorder characterized by excessive oxidative stress-associated cell death; and administering to the individual a composition comprising an N-phenyl-2-pyrimidine-amine in an amount effective to reduce or prevent oxidative stress-associated cell death in the individual (see claim 1). Applicants have elected STI571 (claim 2) as the N-phenyl-2-pyrimidine amine, and ischemia/reperfusion injury (claim 17) as the disorder characterized by excessive oxidative stress-associated cell death.

Gambacorti teaches compositions of a tyrosine kinase inhbitor with an organic compound capable of binding to alpha-1-acidic glycoprotein for the treatment of proliferative diseases (e.g., tumor diseases), especially those that can be treated by inhibition of abl- receptor-tyrosine kinase activity (abstract). The preferred tyrosine kinase inhibitor is STI571 (page 4).

Gambacorti does not teach reducing oxidative stress-associated cell death with said composition, or treatment of individuals diagnosed as having or being at risk of

contracting a disorder characterized by excessive oxidative stress-associated cell death.

Kumar teaches that c-Abl tyrosine kinase is activated in the response of cells to oxidative stress; said stress (from reactive oxygen species, or ROS) induces targeting of the c-Abl to mitochondria, which is associated with ROS-induced loss of mitochondrial transmembrane potential (abstract). Additionally, said c-Abl is necessary for activation of a necrosis-like cell death (abstract) as well as apoptosis (page 17281), and thus the c-Abl kinase mediates mitochondrial dysfunction and cell death (abstract).

Kufe teaches that compounds which modulate the mitochondrial translocation of a protein (such as c-Abl) can be used to modulate levels of apoptosis, and thus can be used to treat disorders characterized by insufficient apoptosis, e.g., cancer, or excessive apoptosis (see abstract and column 5); examples of disorders associated with excessive cell death are myocardial infarction and stroke, wherein cell death occurs within and outside the central ischemic zone (col. 11, lines 41-47).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select individuals diagnosed with, or at risk for, disorders characterized by excessive cell death and administer STI571 to said individuals; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because administration of abl- inhibitors of tyrosine kinase activity (such as STI571) is known to treat proliferative diseases (i.e., disorders characterized by insufficient apoptosis), as taught by Gambacorti, and the inhibition of tyrosine kinase would also be reasonably expected to reduce cell death, since c-Abl tyrosine kinase activity is known

to mediate cell death, as taught by Kumar. Furthermore, administration of said tyrosine kinase inhibitors is known to modulate apoptosis and therefore be useful to treat diseases characterized by excessive or insufficient apoptosis, as taught by Kufe et al, and therefore one skilled in the art would be motivated to select individuals diagnosed as having or being at risk of contracting a disorder characterized by excessive cell death. One skilled in the art would reasonably expect success from the administration of STI571 to reduce oxidative stress-associated cell death because Gambacorti, Kumar, and Kufe are all drawn to the problem of modulating cell death via the role of abl-tyrosine kinase activity.

Regarding claims 3 and 4, Kufe teaches that treatment of individuals with disorders characterized by excessive apoptosis, such as neurological disorders, as well as myocardial infarction and stroke (see col. 5, lines 41-50 and col. 11, lines 41-47).

Regarding claims 17 and 18, Kufe teaches that two common disorders associated with cell death are myocardial infarction and stroke, wherein cell death occurs within and outside the central ischemic zone (col. 11, lines 41-47).

Regarding claims 21 and 22, Gambacorti et al teach that a second compound administered with STI 571 may be selected from anticoagulants (see pages 18 and 19).

Regarding claims 23 and 24, the steps of testing for ischemia/reperfusion injury after administering the composition and again administering the composition after said test, amount to standard protocols of adjusting the dose of a medication after treatment is started in an individual based on the efficacy of the initial dose, and are well within the

purview of the skilled artisan and thus do not impart patentability to the claims, absent evidence to the contrary.

Regarding claim 27, Kumar teaches assessment of apoptosis and necrosis by flow cytometry (page 17282), and therefore the step of evaluating the viability of cardiovascular tissue of the individual after administration of the composition is within the purview of the skilled artisan and does not impart patentability to the claims, absent evidence to the contrary.

Regarding claims 28 and 29, Gambacorti teaches that the compositions may be administered parenterally (page 33), such as infusion solutions (page 36). Additionally, Kufe teaches that the compounds may be formulated for parenteral administration by injection, for example, by bolus injection or continuous infusion (col. 12, lines 36-38).

14. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambacorti in view of Kumar and Kufe as applied to claims 1-4, 17, 18, 21-24, and 27-29 above, and further in view of Robinson et al (US Patent 5,135,945).

Claims 19 and 20 of the claimed invention are drawn to the method of claim 17, wherein the individual has been diagnosed as having an organ transplant surgery (claim 19) or has undergone or is undergoing coronary bypass surgery (claim 20).

The invention of the combined references is delineated above (see paragraph 13).

The invention of the combined references does not specifically teach that the disorder is organ transplant surgery or coronary bypass surgery.

Robinson et al generally teach that reperfusion damage due to oxygen-derived free radicals causes cell death in tissues, and that this situation arises when total or partial blockade of blood supply to tissues is removed, such as during by-pass, organ transplant, coronary infarct, stroke, and the like (see col. 6, line 60 – col. 7, line 5).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select an individual who has undergone or is undergoing organ transplant surgery or coronary bypass surgery and administer STI571 to reduce oxidative stress-associated cell death; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because the conditions of organ transplant surgery and coronary bypass surgery are known to cause reperfusion damage and cell death in tissues, as taught by Robinson et al, and therefore reasonably read on disorders characterized by excessive apoptosis, as taught by Kufe et al.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

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